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CHEMOTHERAPEUTIC AGENTS FOR CANCER

Despite the numerous articles in both medical and lay publications on advances in the chemotherapy of malignant tumors, the mainstays of treatment are still surgery and radiotherapy. No drug yet discovered is so effective against cancer that it can replace the older therapies. Though they seldom produce cures, however, many different anticancer agents are able — in some patients — to give relief of pain, temporary disappearance of tumor masses, prevention of metastases following surgery, and significant increase in survival time. The first of a series of appraisals of the various anticancer drugs, this one on the alkylating chemicals, follows. (For the treatment of lymphomas, see The Medical Letter, 2:25, 1960.)

FREQUENCY OF REMISSION - Carcinomas of the breast and the ovary, certain testicular tumors, and choriocarcinoma are the only solid tumors with which anticancer drugs, including the alkylating agents, give hope of clinical remission for periods of months or more in at least 20 per cent of the patients. The drugs are much less effective with other tumors.

The gap between toxic and therapeutic doses with anticancer drugs, especially the alkylating agents, is at best very narrow and since the toxic effects are often delayed and cumulative, the determination of safe dosage levels is difficult. For investigative purposes, most compounds are given until marked toxicity is observed, but practicing physicians should try to keep doses below the levels which produce severe toxic reactions. If the recommended doses do not give a significant response, larger doses will seldom help.

CAUTIONS - Combinations of alkylating and other anticancer drugs are dangerous unless proper dosage adjustments are made, and it is generally hazardous to combine these drugs with irradiation or with corticosteroids. When they are used to treat exfoliating or ulcerating lesions while the patient is undergoing severe stress, as in surgery, the risk of tissue necrosis, hemorrhage, and the initiation of systemic sepsis must be kept in mind. To avoid overtreating the obese and undertreating the thin patient, adult dosage for all anticancer drugs should be calculated according to ideal weight (Metropolitan Life tables), not actual body weight. (For children, dosage is commonly related to body surface area.) Dosage should also be adjusted to take into account the clinical condition of the patient, previous treatment and the state of the bone marrow.

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Of the parenteral alkylating agents, nitrogen mustard has been in longest use and it is the drug of first choice with many clinicians when rapid action is desired. Chlorambucil (Leukeran — Burroughs Wellcome) has the advantage of being given orally, and it is as effective as other alkylating agents for patients with carcinoma of the testes or the ovary. When one alkylating agent is ineffective or resistance to it develops, other alkylating agents will also be ineffective, and other classes of drugs should be tried, such as antimetabolites, steroids and antibiotic agents.

Nitrogen mustard (Mechlorethamine, USP; Mustargen — Merck) is used to treat carcinomas of the ovary, the breast, and occasionally the lung. (It is also used for the control of Hodgkin's disease and other lymphomas, as well as malignant pleural and peritoneal effusions.) The limiting toxicity of nitrogen mustard is bone-marrow depression, which means that constant observation of the patient is necessary to prevent fatal overdosage. Pretreatment with barbiturates is recommended to prevent severe nausea and vomiting. The usual adult dosage for each course is a total of 0.4 mg./kg. (ideal weight) in two successive daily doses of 0.2 mg./kg. It is administered by injection into the tubing of a running saline infusion. Direct intravenous injection may result in severe local inflammation and necrosis if any of the drug escapes into the tissues. Administration by perfusion of isolated body areas is still in the stage of investigation.

Triethylenethiophosphoramide (Thio-TEPA — Lederle) has effected clinical remission of metastatic breast cancer in from 10 per cent of cases in some studies to about 40 per cent in others. Somewhat better results can be expected in the treatment of advanced ovarian cancer. Remissions of variable duration are reported in about 5 per cent of patients with melanoma, carcinoma of the lung, and various sarcomas; regression of a gastrointestinal malignancy is rare.

An optimal dosage schedule has not been determined for Thio-TEPA. The usual adult dosage, administered intravenously for rapid effect, is 1 to 1.2 mg./kg. spread over a period of 5 or 6 days at the rate of 0.2 mg./kg./day. With debilitated patients, 0.2 mg./kg. should be given on alternate days over a period of 10 days. Thio-TEPA is also used orally with the same dosages based on ideal body weight. Repeated courses at intervals of not less than a month are considered preferable to prolonged maintenance therapy, and in general they are indicated only when tumor regrowth is confirmed by clinical observation. If maintenance therapy is used, the adult dose should be about 0.2 mg./kg. of ideal body weight each week, with a weekly white count and clinical evaluation. If the count falls below 3,000, if infection is present, or if there is no inhibition of tumor growth in four weeks, treatment should be discontinued.

As with nitrogen mustard, the most serious side effect of Thio-TEPA is depression of the bone marrow, with increased susceptibility to infection and bleeding. Significant depression of the white count may occur as early as the third day after therapy is started, or as much as two weeks later. White counts should be done on alternate days during intensive therapy, and weekly if maintenance doses are being given. Early rapid depression of the white count is ominous, and a sharp drop in the white count is often more significant than the actual level. Therapy should seldom be continued when the count falls below 3,000. Blood platelet levels also should be closely watched. Nausea is less common than with nitrogen

mustard, and vomiting can usually be controlled by pretreatment sedation. Since ulcerating lesions are commonly infected, their presence may contraindicate therapy; they may cause systemic infection as the leucocyte level is depressed, or hemorrhage if the platelet count falls below 50,000.

Triethylenemelamine, USP (TEM — Lederle) is similar to Thio-TEPA in properties and effects, but it has been largely supplanted by Thio-TEPA. A noteworthy use of TEM (though other alkylating agents can also be used) is as an adjunct to irradiation for retinoblastoma (A. B. Reese, et al., AMA Arch. Ophth., 60: 897, 1958).

Chlorambucil (Leukeran — Burroughs Wellcome) has been effectively used for carcinomas of the ovary as well as for chronic lymphatic leukemias and lymphomas. It is well tolerated, and the mild toxic reactions are relatively slow to develop. It has the additional advantage of oral administration. The usual dose is 0.1 or 0.2 mg./kg./day. Recent studies of the use of the combination of chlorambucil, Actinomycin D and methotrexate in the management of testicular tumors have shown remission rates of about 35 per cent, with prolonged disappearance of metastases in about 10 per cent of the patients. Unfortunately, Leukeran is not very effective in other solid tumors.

Cyclophosphamide (Cytoxan — Mead Johnson; Endoxan [British]) is generally similar in antitumor spectrum, effectiveness, and toxic effects to nitrogen mustard and other alkylating agents. It does, however, cause temporary alopecia in about 20 to 40 per cent of patients. The recommended intravenous dosage is 3.5 to 5 mg./kg./day for 10 days. There is insufficient experience with oral dosage of this drug to make its use advisable.

Busulfan (Myleran — Burroughs Wellcome) is useful chiefly in chronic myelocytic leukemia, myelofibrosis and polycythemia vera, and not in solid tumors.

DIAL SOAP AND STAPHYLOCOCCAL INFECTIONS

The regular daily use of soaps containing antibacterial agents such as hexachlorophene, trichlorocarbanilide, and bithionol will, as is well known, reduce but not eliminate the resident bacterial population of the normal skin. And because of their effect on bacteria, such soaps are superior to ordinary soaps as deodorants. They may also be helpful to some patients suffering from repeated attacks of folliculitis or furuncles. Furthermore, there is no evidence that their use promotes the emergence or development of resistant strains of staphylococcus or superinfection by other microorganisms.

Now, advertisements for Dial bar soap (which contains 0.5 per cent hexachlorophene and 0.5 per cent trichlorocarbanilide) recommend its "routine use by physicians, nurses and patients... as aid in eliminating one cause of [Staphylococcus aureus] infection in hospitals." Neither Dial nor any other soap, with or without an antibacterial agent, will eliminate Staphylococcus aureus or other microorganisms from the skin (which is not a major source of Staphylococcus aureus infection in hospitals), and there is no evidence that the use of Dial or any

other antibacterial soap by hospital personnel and patients will reduce the incidence of staphylococcal infections. Nevertheless, any reduction of potentially pathogenic organisms in the hospital environment is desirable, and Dial and other soaps containing antibacterial agents might well be substituted for ordinary soaps for routine use by hospital personnel and patients.

INFLUENZA

Despite press reports suggesting the likelihood of a severe influenza epidemic this fall and winter, health officials do not anticipate more than a moderate increase over last year in the number of cases. As in previous years, however, physicians should urge immediate vaccination for patients with heart and pulmonary disease, diabetes, and other chronic illnesses; all persons over 65 years of age; and pregnant women. Others not in these groups may want the protection of the vaccine; its use is contraindicated only in persons allergic to egg or chicken. Persons who have had previous immunization need only one injection of the polyvalent (types A and B) influenza vaccine. Those without previous immunization should receive a booster dose two months later.

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